

Attorney Docket No.: INT-0004
Inventors: Mattern et al.
Serial No.: 10/002,653
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REMARKS

Claims 2-9 and 11-16 are pending in the instant application. Claims 2-9 and 11-16 have been rejected. New claims 17, 18, 19 and 20 have been added. Support for these claims is provided in the specification at page 14 and Example 3 and in claims 2, 9 and 11. Thus, no new matter is added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims 2-9 and 11-16 under 35 U.S.C. 103(a) and Claims 2-8 and 12-16 under 35 U.S.C. 102(b)

The rejection of claims 2-9 and 11-16 under 35 U.S.C. 103(a) as being unpatentable over Yannas et al. (U.S. Patent 4,060,081) or Yannas et al. (U.S. Patent 4,280,954) in view of Li (U.S. Patent 5,675,290) has been maintained.

The rejection of claims 2-8 and 12-16 under 35 U.S.C. 102(b) as being anticipated by Yannas et al. ('081) or ('954) has also been maintained.

Applicants respectfully traverse these rejections.

At the outset, Applicants respectfully disagree with the Examiner's characterization of teachings of sterilization techniques in the cited prior art references.

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Contrary to the Examiner's suggestion, col. 12, line 52 of Yannas ('081) does not disclose a composition containing a collagen and glycosaminoglycan co-precipitate cross-linked with glutaraldehyde and which can be sterilized with irradiation. Instead, teachings at col. 12, line 52 of the '081 patent are related to sterilization techniques of the moisture control layer, not the cross-linked collagen-GAG layer. Specifically, col. 12, lines 47-53 of the '081 patent states:

[a]dditionally, it is advantageous if the moisture control layer is capable of being sterilized, i.e. of being subjected to physical or chemical treatment that kills bacteria and bacterial spores on its surface. Suitable sterilization techniques include dry heat, exposure to ethylene oxide, irradiation, immersion in glutaraldehyde solution, etc.

The moisture control layer is described further at col. 13 as a synthetic polymeric material such as silicone.

Further, teachings of Yannas ('954) at col. 23, lines 19-27 provides details of chemical sterilization methods, not simply the broad concept that "the cross-linked co-precipitate may be sterilized" as implied by the Examiner. There is no teaching or suggestion of sterilization by irradiation in the '954 patent.

Finally, the Examiner's suggestion that Li teaches electron beams as an "alternative to gamma irradiation" is a mischaracterization of statements made by Li. Specifically at

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page 3 of the Office Action the Examiner cites col. 6, lines 48-52 and col. 1 lines 28-30 of Li as teaching "[a]lternative to gamma-irradiation, electron beams may be used for sterilizing." Further at page 3, the Examiner suggests that Li discloses "electron beam irradiation as an alternative to gamma irradiation for sterilizing an implant made of a cross linked co-precipitate of collagen glycosaminoglycan." At page 5 of the Office Action the Examiner again characterizes Li as "suggesting electron beam irradiation as an alternative to gamma irradiation."

However, Li actually states at col. 1, lines 28-30 that "[a]n alternative to ethylene oxide sterilization is gamma irradiation or, less frequently, irradiation with electron beams." Further, at col. 6, lines 48-52, Li et al. states:

For example, while the gamma ray limitation is included in all of the appending claims, both treatment of a hydrated implant for irradiation with electron beam preparation obtained from such treatment are indeed contemplated embodiments of this invention under the doctrine of equivalents.

Thus, Li clearly teaches electron beam irradiation to be an equivalent sterilization process to gamma irradiation, not an alternative.

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Applicants have already submitted two separate statements by scientists in this art field establishing that gamma irradiation is not a useful sterilization technique for collagen-GAG matrices. Specifically, in paragraph 3 of Donald Nociolo's Declaration he states that:

in experiments performed at Integra, we found that gamma irradiation was not an acceptable means for sterilization of our particular collagen-GAG matrix.

In the experiments performed at Integra, the collagen-GAG matrix was gamma irradiated at a minimum dose of 18 kgray (a dose falling within the 15 to 35 kGy range taught by Li et al.). See paragraph 3 of Donald Nociolo's Declaration. The resulting product failed to meet multiple release specifications during its stability tests. See paragraph 3 of Donald Nociolo's Declaration.

In paragraph 3 of Timothy Malaney's Declaration, he states that:

initial tests of gamma sterilization or their product [a cross-linked collagen and chondroitin-6-sulfate matrix; see paragraph 2 of Timothy Malaney's Declaration] were satisfactory but the product did not perform adequately over time. Among the results noted were tearing of the collagen matrix associated with a sticky silicone bilayer and an unpleasant odor associated with the product upon opening.

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Further, if the Examiner believes it would advance the prosecution of this case, Applicants can submit yet a third Declaration by Dr. John Burke. Dr. Burke collaborated with Ioannis Yannas in studies of the synthetic skin product ultimately developed from the collagen-GAG matrices described in Yannas Patents '081 and '954 (see paragraph 2 of Dr. Burke's Declaration). He realized the need for a terminally sterilized synthetic skin product and was aware of the failed attempts of Dr. Yannas to produce a terminally sterilized end product which retained characteristics to function as a structural support for cell and tissue ingrowth by gamma irradiation of Dr. Yannas' collagen-GAG matrix.

Evidence of these prior failed attempts to produce a terminally sterilizable matrix via gamma radiation is clearly relevant to the issue of obviousness and must be considered. See MPEP 2141.

Li's teachings of electron beam radiation to be an equivalent treatment to gamma radiation clearly teaches away from any expectation of success that electron beam radiation would provide a useful terminal sterilization means for collagen-GAG matrices given the objective evidence set forth in these three Declarations relating to failure of others with

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respect to terminal sterilization of a collagen/GAG matrix with gamma irradiation.

Further, MPEP 2146 and the Court in *In re Hedges* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986) make clear, the totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness.

Furthermore, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams* 383 U.S. 39, 52, 148 USPQ 479, 484 (1966). If teachings of Li et al. are representative of accepted wisdom, namely that electron beam radiation is an equivalent to gamma radiation; those skilled in the art would be discouraged from using electron beam radiation as a terminal sterilization technique, given the multiple failed attempts with gamma radiation described in the Declarations of Donald Nociolo, Timothy Malaney and John Burke (to be submitted upon request of the Examiner). They would be particularly discouraged from using electron beam irradiation doses of 15 to 35 kGY given that these gamma irradiation doses resulted in matrices that did not retain characteristics to function as a structural support for cell and tissue ingrowth.

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Further, Applicants respectfully disagree with the Examiner's suggestion that the cross-linking conditions of Yannas et al. ('081) or (954) will inherently provide a cross-linkage density as claimed to stabilize for electron beam radiation. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2dd 1955, 1957 (Fed. Circ. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-582, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be recognized by persons of ordinary skill. Inherency, however, cannot be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

As discussed in the amendment filed October 7, 2004, the specific cross-linking conditions taught by Yannas et al. are

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different from those conditions which stabilize the scaffold or matrix of the present invention toward electron beam radiation. Thus, a cross-linking density which stabilizes the scaffold or matrix to electron beam radiation is not necessarily present in the matrices cross-linked in accordance with teachings of Yannas et al. The fact that a cross-linking density which stabilizes the scaffold or matrix to electron beam radiation may result upon optimization of cross-linking conditions taught by Yannas or from a given set of circumstances in Yannas is not sufficient to establish inherency.

MPEP 2131 is clear; a claim is anticipated only if each and every element as set forth in the claims is found either expressly or inherently described in a single prior art references. Neither Yannas ('081) nor Yannas {954} expressly teach a scaffold or matrix comprising a collagen and glycosaminoglycan co-precipitate cross-linked with glutaraldehyde at a density of cross-linkage and under conditions which stabilize the scaffold or matrix toward electron beam radiation at about 15 to about 80 kGy so that the matrix or scaffold retains characteristics to function as a structural support for cell and tissue ingrowth. Further, since Yannas ('081) and ('954) teach specific cross-linking conditions

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different from those conditions which stabilize the scaffold or matrix of the present invention toward electron beam radiation, a cross-linking density which stabilizes the scaffold or matrix to electron beam radiation is not necessarily present in the matrices of Yannas et al. Thus, each and every element of the instant claimed invention is not inherently described in either Yannas ('081) or Yannas ('954).

Therefore the instant claimed invention cannot be anticipated by Yannas ('081) or Yannas ('954).

Further, MPEP 2143.02 is quite clear; at least some degree of predictability is required to render an invention obvious. Clearly the combination of Li et al. and Yannas ('081) and ('954) fail to provide any degree of predictability whatsoever with respect to terminal sterilization via electron beam radiation, particularly in light of evidence presented by Applicants in the sworn statements of three individuals highly skilled in this art regarding multiple failed attempts with gamma irradiation. Further, suggestions in Yannas relating to optimization of cross-linking density for solubility and/or resistance to resumption are irrelevant to the instant invention wherein cross-linking conditions stabilized the matrix to a terminal sterilization technique, namely electron beam radiation.

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At most this combination or references provides an "obvious to try" rationale wherein the skilled artisan varies all parameters or tries each of numerous possible choices until one possibly arrives at a successful result, where the prior art gave no indication of which parameters where critical or no direction as to which of many possible choices was likely to be successful with respect to stabilization to a terminal sterilization method. This type of rejection is clearly improper. See MPEP 2145.

Thus, withdrawal of the rejection of claims 2-9 and 11-16 under 35 U.S.C. 103 and the rejection of claims 2-8 and 12-16 under 35 U.S.C. 102(b) is therefore respectfully requested.

II. New Claims 17-20

In an earnest effort to further distinguish the present invention from the cited prior art teachings of Li et al. and Yannas et al., Applicants have added new claims 17 and 18 which include the limitation that the matrix further comprises a silicone layer applied to the collagen and glycosaminoglycan co-precipitate prior to cross-linking of the collagen and glycosaminoglycan co-precipitate. The bilayer which forms between the co-precipitate and the silicone prior to cross-

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linkage is important to the long-term stability of matrices of this embodiment following electron beam irradiation. Support for these claims is provided in Example 3 and claim 2.

Applicants have also added new claim 19 drawn to a method for producing a terminally sterilized matrix or scaffold which comprises producing a scaffold or matrix comprising a collagen and glycosaminoglycan co-precipitate cross-linked with glutaraldehyde at a density of cross-linkage and under conditions which stabilize the scaffold or matrix toward electron beam radiation at about 15 to about 80 kGy so that the matrix or scaffold retains characteristics to function as a structural support for cell and tissue ingrowth; sealing the composition in a package; and exposing the composition in the sealed package to electron beam radiation and new claim 20 drawn to terminally sterilized matrix or scaffold produced by the method of claim 19.

None of the cited prior art references teach or suggest a matrix wherein a silicone layer has been applied prior to cross-linking of the collagen-GAG matrix as set forth in claims 17 and 18. Instead, both Yannas references make clear that a silicone layer is adhered to the cross-linked collagen-GAG layer.

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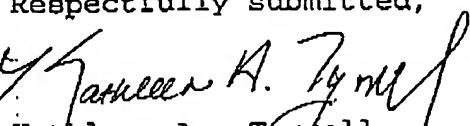
Further, none of the cited prior art references teach all the limitations nor provide any reasonable expectation of success with respect to producing a terminally sterilized matrix as set forth in claims 19 and 20.

Thus, these references, which do not teach or suggest all the limitations of claims 17-20, nor provide any reasonable expectation of success with respect to claim 17-20, neither anticipate nor render obvious new claims 17-20.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,


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